Understanding iSTOPMM: Iceland Screens, Treats, or Prevents Multiple Myeloma with Dr. Sigurour Yngvi Kristinsson

iStopMM initiative may be one of most important events in modern day myeloma care. As part of the iStopMM study, 140,000 Icelanders over the age of 40 will have their blood samples tested for the precursor to multiple myeloma, or MGUS (monoclonal gammopathy of undetermined significance). We have Dr. Siguror Kristinsson of the University of Iceland discuss this exciting and groundbreaking study with us.

Full Transcript:

Priya Menon – Good morning and welcome to CureTalks. I am Priya Menon, Scientific Media Editor of CureTalks, joining you from India; and today we are talking about multiple myeloma. This is CureTalks' 112th episode. On the panel are myeloma survivors and advocates, Yelak Biru, Matt Goldman, and Cynthia Chmielewski. The talk is being co-hosted by myeloma survivor and advocate and editor of myelomasurvival.com, Gary Petersen. This is our third talk in the series on high-risk smoldering myeloma. In the previous episodes, we spoke with Dr. Shaji Kumar from Mayo Clinic regarding the ASCENT clinical trial; Dr. San Miguel from University of Nevarra about his team's investigations into high-risk smoldering myeloma and probable cure. For this third talk today, we have with us Dr. Sigurdur Kristinsson from University of Iceland, discussing the iSTOPMM initiative. As part of the iSTOPMM study, 140,000 Icelanders over the age of 40 will have their blood samples tested for the precursor to multiple myeloma or monoclonal gammopathy of undetermined significance, MGUS. In the coming hour, we will be discussing this exciting and groundbreaking study. Before I hand over to Gary, I would like to remind the listeners that we will be addressing questions sent in to us the end of the show. If you would like to ask a question live, please press 1 on your keypads and let us know. You may also email them to priya@trialx.com or post them on the CureTalks' website. Gary, its over to you.

Gary Petersen – All right. Thanks, Priya, and thank you so much for bringing this forum for all of myeloma patients. We certainly do appreciate your continued support. While this is a very exciting CureTalks for me and Dr. Sigurdur Kristinsson is the Professor of the Faculty of Medicine at the University of Iceland in the Department of Hematology at Landspítali University Hospital, Iceland, and recently received a major grant to identify and treat precursor of blood cancer before disease develops. Now, he initiated this project and got the support of the International Myeloma Foundation to help fund it, but we certainly do thank you for your vision with regard to taking on this…, this cure. Recently, I saw Dr. Durie who, you know, was talking very much about this being an excellent program and one that might lead to a cure. The IMF Chairman and Co-founder of the IMF is who Dr. Durie is and he has the IMF's Black Swan Initiative and he will be provided a grant with that initiative, but the Black Swan Research Initiative is a groundbreaking research project in curing myeloma and Dr. Durie states that we are extremely pleased to be able to support iSTOPMM study as we strongly believe that early diagnosis and treatment can lead to the cure of myeloma. So, thank you, doctor. Dr. Kristinsson, I got to tell you that you are the first Sigurdur I have ever met and I have tried to say your middle name. What is your middle name?

Dr. Sigurdur Kristinsson – Yngvi.

Gary Petersen – Okay. Its Y-N-G-V-I, which is Yngvi as well. We had recently talked with Dr. San Miguel. We also talked with Dr. Kumar and they have provided us some outstanding news about treatments for high-risk smoldering myeloma; however, the big "if" and I mean a big "if" is how do we find it in the early stages and could…, and would you please explain how iSTOP and how it might just be the answer to this big "if."

Dr. Sigurdur Kristinsson – Thank you. Thank you very much for inviting me to this conference. Good

morning! So, the iSTOPMM study which stands for Iceland Screens Treats or Prevents Myeloma and we are actually launching this study tomorrow morning in Iceland and I can go through the details maybe in a while, but there are two ways to diagnose high-risk smoldering myeloma. We are approaching a client who is probably going to be treating these individuals and these are per definition asymptomatic. They have no symptoms. So, either we diagnose them by chance alone or we screen, this is the only way to go. So, we think that since we are approaching the era of treating asymptomatic individuals, we at least have to research that to check the hypothesis that the screening for these precursors is of benefit when it comes to overall survival.

Gary Petersen – Okay and could you explain how its going…, you know, what the elements are of the program?

Dr. Sigurdur Kristinsson – Yeah. Sure. So, what we are doing now, we are sending out information to all individuals that are living in Iceland and are 40 years and older. These are approximately 140,000 people. They will get a purple envelope home with list of information with the protocol and design of the study. We then ask them to go online and visit the homepage of the study, which is mgus.is and there they can provide informed consent using a code that they will get in the envelope. For them, it takes about 1-1/2 to 2 minutes to sign up. Then, what we are doing, we will gather a database with all these individuals that will provide the informed consent. Then, that's pretty much what the individuals have to do because what we are doing here is, we are using a unique way of gathering samples, that is blood samples, from these individuals. So, instead of opening up a big clinic to draw blood, we are utilizing the fact that most individuals in Iceland and many western countries do a blood test for whatever reason during a period of three years. So, once these individuals do a blood test three…, three years following their informed consent, they just need to check their cholesterol or thyroid or acute illness or whatever reason. We will get a sample of their serum to screen for MGUS and myeloma.

Dr. Sigurdur Kristinsson – So, we have in Iceland 35 laboratories that draw blood and we have collaboration with each and every one of them. So, it doesn't matter where in the country these individuals do their blood sample, they will get this extra sample. This will be sent to us here in capital of Iceland, Reykjavík, through the University, then the serum will be sent to the Binding Site in Birmingham, UK, which is a major sponsor of the study. They will perform protein electrophoresis and free light chain analysis. Now, after that, we will then screen all these individuals, say 140,000 people. We have done a small pilot study here, so you can see that about 4% of the Icelandic population in this age group actually have an MGUS. So, in all of these, they will get a lot of MGUS individuals. These individuals that have MGUS, they will enter a randomized clinical trial.

Dr. Sigurdur Kristinsson – So, those with the MGUS will be randomized to one of three arms. Arm 1, we will not do any further workup or followup. Arm 2, we will do what is currently recommended by the International Myeloma Working Group; and then arm 3, we will do a more intense workup, more intense followup, and we will be a little more aggressive when it comes to bone marrow sampling because we want to capture these individuals as soon as they enter the smoldering phase, hopefully and through another clinical trial which will be a treated protocol for smoldering myeloma.

Sigurdur Kristinsson – So, this is the main outcome of the study. We have a lot of other things that we are doing. We have a unique identifier or personal identifier here, so we have like a source of security provision that everyone uses everyday and this is used for card allotment and health registers. So, for those individuals, regardless if they have MGUS or if they don't have MGUS, we will get the information of all diseases that they have developed before the maintenance study and after the study and during the followup of the study. All this is whether diagnosed in hospitals or outpatient clinics and with general practitioner's office. We will get information on every prescription drug that they get. We will get the information on every cancer that has been diagnosed before and after the study and…, and we will get the information of lifestyle status of all individuals regardless if they are alive or dead and if they have…, if they are deceased, we will get the information on causes of death.

Dr. Sigurdur Kristinsson – So, this is on the ethical issue. One really important issue is that they want to analyze quality of life of these individuals because the literature is actually very, very sparse when it comes to quality of life of individuals in screening purpose because one outcome of this study could be that the screening is beneficial when it comes to survival, but it causes anxiety and depression. So, we will do that in all Icelanders before and after the study. We will check their quality of life, anxiety, and then level of happiness and then this will be done throughout the study during their 5 or 7 years of followups. So, we can follow individuals that have MGUS and those that do not have MGUS instead of how their quality of life changes throughout the period of the study. Then, we will also do a very intensive biometric. Since we are doing a lot of bone marrow, blood work, and urine, we will do a lot of biometric for future studies. So, if you come up with a new method that might be of importance when it comes to prognosis or progression or whatever, we will be able to go to the freezer in 5 or 10 or 15 years and check…, and check samples for whatever reason we can think of basically.

Gary Petersen – Okay and you have actually answered most of my second question, but the part that wasn't answered would be, in fact, this is more than just blood testing, you are doing a lot more and you have outlined that a lot more but one of the things that Dr. Durie had mentioned in his interview on YouTube was that parts of the project will include the use of the aggressive cure treatment protocols. Is that correct or did you get that wrong?

Dr. Sigurdur Kristinsson – So, that is the plan. We are working on the protocol, so the exact…, the exact design of the treatment trial. So, we have a randomized clinical trial that is only, that is the MGUS, the workup and the followup. Then, we are planning to offer treatments to all individuals in Iceland that will develop smoldering myeloma, all myeloma, active myeloma. So, after treatment, I cannot tell you exact details of the study since this is not approved yet, but this is certainly the plan because if we screen and detect the disease early than still wait for bone lesions or renal failure, then it doesn't make any sense to screen. Early detection has to lead to early treatment, otherwise we can might as well just wait for the patient to enter the clinic with structure, but this is not what we believe in anymore.

Gary Petersen – Yeah and I think that the patient would like to see is that they don't have symptoms.

Dr. Sigurdur Kristinsson – Yes.

Gary Petersen – For example, I had…, I had kidney failure and…, but it would be nice if that didn't happen and I know another person who had a stroke because her blood got very, very thick; and Pat Killingsworth, for example, who is very different than mine had terrible bone pain and had his hips replaced and a bunch of other things. So, we would certainly like to see CRAB, you know, the whole CRAB symptoms that would be a thing of the past and this…, this looks like a role to do that. I know the IMF is supporting to fund it, this program and so they have the cost of testing for each individual, you know what that is?

Dr. Sigurdur Kristinsson – No and…. So, that's actually one of the main outcomes of the study, that is the cost effectiveness and this is something that we need to, you know, wait for the results. There are ways to conflict this, there are like quality analysis stuff like this is a science of its own. So, what we are trying to do is, since we are using infrastructure here, we are not drawing blood specifically for this study and this has not been done in any screening program anywhere in the world. We don't actually get the sample to do the screening for any pre-malignancy. So, we are doing everything we can to lower the cost, but in the end it will cost a lot. So, we will have to show that this is really beneficial for the economy in Iceland and anywhere else in the world and to see that we have to show that this is effective and this leads to prolonged survival, overall survival, myeloma survival and that it doesn't decrease quality of life and it doesn't get Iceland to go into bankruptcy. We were pretty close few years ago, but we have recovered now. So, this is something that is a very important point, but I cannot give you a price tag on that.

Gary Petersen – Okay. I know that when I looked at, you know, some of the information that I could find for Medicare that it was about 150 bucks you ask to do all the tests once.

Dr. Sigurdur Kristinsson – Yes.

Gary Petersen – So, you know, given…, given that, I also went through and did my own quality analysis and I found that it was about 16,100 dollars per life year saved, so it was an unbelievably great payback compared to, you know, all other drugs that we use now and and I also posted on my website at some time…

Dr. Sigurdur Kristinsson – Okay.

Gary Petersen – …in the near future.

Dr. Sigurdur Kristinsson – I don't believe that. You might get the group discounts. Right?

Gary Petersen – I am sure you will, you know, its only to do one at a time, 150 bucks, but I am sure, you know, that for you its going to be 140,000; for the United States, it would be 149 million. So, somehow I think they'd get a discount.

Dr. Sigurdur Kristinsson – And then, of course, we have to see, maybe there are some subgroups that we want to focus on, maybe that's one of the results of the study that we should…, maybe we don't need to screen 40-year-olds, maybe we should screen 60 to 80-year-olds, maybe we should focus on those with a family history, maybe we should…, there are some papers assume that there is a social history of obesity, so maybe that is something. We know that people of black race have higher incidence…, Doppler incidents of myeloma with MGUS, so maybe those are groups that we need to focus on. So, we have to take that into account as well, but for Iceland we are screening everyone 40 years and older and then we will have a lot of data to analyze later on.

Gary Petersen – All right. It will provide a lot of insights into what needs to follow from here on?

Dr. Sigurdur Kristinsson – Yeah. Yeah. Yeah.

Gary Petersen – Yelak, are you online? Do you have questions for the doctor?

Yelak Biru – I am.

Gary Petersen – All right. Yelak, please.

Yelak Biru – Thank you. Thanks, Gary. Dr. Kristinsson, congratulations and I want to start by saying congratulations on the success that Iceland had during the Euro cup, 2016.

Dr. Sigurdur Kristinsson – Thank you.

Yelak Biru – For me, it's really the testament that even if you are small, with strategic plan, determination, and collaboration, you can achieve great success. It reminds me of actually the myeloma community that specifically I spoke myeloma or iSTOPMM, it certainly is groundbreaking, but this is still voluntary from what I understand, you know, that the Iceland community has to go up into the program. How are you finding to convince Icelanders who willingly opt into the program?

Dr. Sigurdur Kristinsson – Yeah. Yeah. Yeah. So, the participants have to sign the informed consent. So, we are using several approaches for this. Icelanders are very keen on participating in big studies like this. So, we know that from the Icelandic Cancer Society, which is one of the major collaborators with us here. They have almost 80% participation rate. Then, we have other major research institutions that have similar…, that gives 75% to 80% participation rate and usually that is for studies that are much more difficult and it demands participants to do a lot of tests and spend a few days answering different questions on quality of life and everything. So, we are going to have a campaign here in Iceland where we have already approached the media and we would be able to… Since Iceland is a small country, it is not that difficult to get, you know,

like on national TV and so for that we have sent out a brochure that is, I think, quite good with detailed information. We have the first female President of the world. She is endorsing the study. Actually, finally, once we have asked people to participate, we will send out another approach here a few days after that and then the ones that haven't replied either yes or no, we will actually sit down and call them. So, we are just going to sit on it, spend two months calling every Icelander and asking them to participate. So, that is the plan.

Yelak Biru – Is there a time frame where you expect the program not only to kick but for the people to start signing up into the program? Is it 2016, 2017?

Dr. Sigurdur Kristinsson – Yeah. So, tomorrow they will be able to start with signing up, tomorrow morning, and then we will…, actually it will be open for informed consent for three years because that is the time length we will take to get all the samples.

Yelak Biru – Okay.

Dr. Sigurdur Kristinsson – Between all these studies, we will have a campaign, so we will try to own the…, you know, the talk of the street here in Iceland. So, people should be like… In the background, we want them to be talking about the iSTOPMM study and so we anticipate that most of the individuals that actually sign up by the end of first three weeks. Then, we have plans where we go out to media again with advertisements. Then, we anticipate that we will have another week of participation and then finally when we call them like three months from…., from now, we can see that we will get or hope at least 80% participation.

Yelak Biru – So, preventing high-risk myeloma from progressing this way, we will start at the MGUS or smoldering phase. All that we are speaking about and having questions today are way past smoldering and most of them are being treated for myeloma and. How do you see this iSTOPMM helping enhance the strategic plans to cure myeloma in the future?

Dr. Sigurdur Kristinsson – Yes. So, we know that every myeloma…, active myeloma, actually goes through the precursor stages. So, they go from MGUS to smoldering to active myeloma. Obviously, we will…, using the genetic screening, we will probably capture some with active myeloma and these will be offered three days of treatment according to standard of care or perhaps a clinical trial, but the remaining, those that will have this diagnosed in two or three or four years with active myeloma, due to renal failure, fractures, anemia, or something like that, those will hopefully be captured in this screening program. So, before they actually are diagnosed with active myeloma, hopefully a few years, we will be able to intervene and reverse or what we want this present myeloma rather than treat it.

Yelak Biru – Okay.

Dr. Sigurdur Kristinsson – And some of the people think that we know that active myeloma is genetically very heterogeneous and complicated once it is diagnosed, whereas smoldering myeloma or MGUS is lesser heterogeneous. So, we will probably not have one magic bullet for killing all myeloma cells. We will probably always have to have a combination therapy, but at least in theory we do acknowledge its true. In reality, my patients will cure not myeloma, the early stage, because it has differentiated to a complicated disease which is still incurable.

Yelak Biru – Do you anticipate some of the study results being used to find better treatment for those that have…., that already have the myeloma has progressed to full-blown myeloma?

Dr. Sigurdur Kristinsson – Excuse me?

Yelak Biru – So, the results of the study, do you…, do you anticipate the results from iSTOPMM, some of them being used to find, take up treatment for those patients that have full-blown myeloma.

Dr. Sigurdur Kristinsson – I mean, its possible. We were…, we will pretty much diagnose any myeloma patients in Iceland during this screening program. So, we will get information, how is to have uniform aggressive treatment, hopefully with the best available agents. So, I mean…, but this is not a randomized clinical trial for the optimal treatment of all active myeloma. There are other studies besides that will answer that question. We will not have two different treatments done for active myeloma. We are…, we are believing in early detection, early and upfront treatment, everyone gets the same and hopefully we can cure some or even a lot of smoldering myeloma. Then, what is the best treatment for active myeloma? Then, we have to do a randomized clinical trial with standard of care and some novel agents.

Yelak Biru – Okay. So, Gary, my last question of the course, but I think you have already kind of covered that, so maybe you can go to the next panel member. (Pause) Is that…, is that Matt?

Matt Goldman – That is Matt. Thanks, Yelak. I am going to say, thanks, doctor. Thanks for your time. I was going to say good morning, but I realized we are all across the…, so good day. I am just…, I am just curious a little bit. Myeloma is a very rare cancer. What was the motivation for this and how were you able to get a national testing program approved?

Dr. Sigurdur Kristinsson – Yeah. So, actually, we have…, we have been thinking about myeloma's answers for many years. So, we have been, you know, thinking about what is the evidence for doing what we are doing. We have evidence for treatment of myeloma, but they are not really prospective studies or there are no prospective studies with different workup and followup strategies in MGUS. So, we were thinking a little bit about that. Do we need to follow MGUS individuals if there is no evidence for that or maybe we should spend our money on something else, like treating another disease like autism or another cancer or whatever. So, we did a study a few years ago where we looked at if followup is of importance for MGUS. So, what we did is, we looked at all myeloma patients diagnosed in Sweden where I was working at the time, about 40,000 patients. When we looked at those with myeloma, that has a known precursor, was diagnosed with MGUS before, compared to those myeloma patients that were not diagnosed with MGUS. We know that everyone has MGUS, but some of the patients are diagnosed with MGUS and some of them just turn up with full-blown myeloma. So, there is no biological difference between the two myeloma patients in the study. Its just that the patients and the physician know they have MGUS and we could see that those that had a precursor diagnosed, they actually had superior survival with 15% longer survival compared to myeloma patients that did not know they had MGUS.

Dr. Sigurdur Kristinsson – There is another study from the US. When you see the database, it has exactly the same results and interestingly, when we looked at those patients based on the amount of M protein, so those that have a low-risk MGUS which will typically not develop into myeloma, most of that low-risk MGUS still caused myeloma, but those have to risk survival of the myeloma patients. So, we think that our study is at least indicative of the importance of followup in…, in high-risk individuals and perhaps those that have low risk, they are probably seeing a physician annually that they would focus on other diseases like their hypertension, diabetes, or whatever and MGUS was sort of lost because of other disease. So, this claims that if MGUS…, if followup for MGUS is important, then probably we would have to think about if screening would be beneficial. So, we had a long discussion about that, a few of us in the myeloma community. Some thought that we should stop the routine screening parameters, others thought that we should not stop routine screening and revisit in between and we thought we should at least study the importance or the benefits of screening. So, that is the background to this study. Then, we talked and had several meetings with the Binding Site that collaborated with us on the aspect of free light chains, then we obviously got the major funding from the IMF from the Black Swan Research Initiative and that has led us to launching the study tomorrow.

Matt Goldman – Okay. So, getting the funding…, we touched on this already, but getting the funding from IMF is probably very important to this moving forward.

Dr. Sigurdur Kristinsson – Yes, yes. This study costs a lot of money. A lot of people are working directly on the project. The campaign will get the individuals to…, to sign up, calling all Icelanders takes a lot of people's

effort and doing bone marrows and blood work to follow every Icelander for 5 or 10 years, this costs a lot. So, we would not have been able to do this without the support from the IMF and the management.

Matt Goldman – Yeah, that's great. Do you know are the rates for myeloma in Iceland comparable more or less than in the US or elsewhere in Europe?

Dr. Sigurdur Kristinsson – Yes. We are…, we are exactly the same as in…, in Western Europe and in the US, so it's about 6 per 100,000.

Matt Goldman – 6 per 100,000?

Dr. Sigurdur Kristinsson – It's exactly the same and…, and MGUS is about 4 percent, so its exactly the same.

Matt Goldman – Okay, thanks. Okay. And then…, and then, finally my last question is…, there is a little feedback. You touched on this already, you touched about quality of life and…, and when you are doing the screening, sort of tracking people and you also mentioned race and gender, but in your screening, are you also looking at trying to go backwards in your tracking results and look at sort of what their lifestyle was previous to even having MGUS or smoldering myeloma to know what have they been exposed to, what sort of conditions have they been living in, that sort of thing.

Dr. Sigurdur Kristinsson – Yeah. So…, so what we are going to be looking at, like, please get your databases. We will, as I talked about it before, get the information on other diseases. So, not only we would look at what happens to those with MGUS compared to those without MGUS when it comes to infections and fractures and thrombosis or whatever have you. We will also be able to look back and analyze if any given disease is a risk factor for getting myeloma and we will also have questions about environmental exposures, socioeconomic status, proper workup, and stuff like that, but this will be done primarily with those MGUS individuals that we meet, because the only people that actually have physical contact with is all the people with MGUS. So, we will include this in the study as well. We will get email addresses from individuals that want to provide their email addresses so that we can also later get, if they have some new great ideas, go back and ask what their request is basically.

Matt Goldman – Okay. So, sometimes when you start analyzing the data, something jumps out at you, you might be able to dig a little deeper and do additional research.

Dr. Sigurdur Kristinsson – Yes. So, we will…, so, we will get the informed consent. Then, we ask for permission to get the participants and ask additional questions. Also, we ask those that do not have MGUS, we ask them for…, to come for visits like 1:1 ratio, so one control for every MGUS individual for biobanking, for flow cytometry and stuff like that and forgot to mention that they also have a great collaboration with Dr. Ola Landgren at the Memorial Sloan-Kettering in the US which will need a lot of declarative science. So, we have build in plan B, C and D, to be able to really gather and squeeze out as much as we can because I don't think that anyone would do another study like this in the coming years.

Matt Goldman – No. Okay, thanks. This is awesome! I know this is something that Gary and others have really been pushing and to see what you're doing is fantastic.

Dr. Sigurdur Kristinsson – Thanks a lot.

Gary Petersen – Okay. Thanks a lot, Matt. Cindy, your question?

Cynthia Chmielewski – Yes, I am here. Can you hear me?

Gary Petersen – Yayy! Cindy is here.

Cynthia Chmielewski – Yeah. I think this is a great study. Thanks for taking part to the doctor and if I ask some questions that have been answered, forgive me, I joined in a little late. So, I…, I think my first question is about once you take a screening, if someone is identified with high-risk smoldering multiple myeloma, as a part of the informed consent form, do they agree to be in a trial immediately or do they still have that choice of watching and waiting?

Dr. Sigurdur Kristinsson – So, they…, they have another choice, to do whatever they want. So, the only thing that they agree by participating in the screening study is to donate blood for screening and if they turn out to have MGUS, then they enter the randomized clinical trial and actually if they already have the clinical treatment trial ready, then those with active myeloma with high risk will be treated according to standard of care. So, what we are resting on now is to ask a treatment trial with not only high-risk smoldering but all smoldering individuals and so the only thing to do is offer the smoldering myeloma patients to enter a treatment trial and that is completely voluntary, of course. If they want to watch and wait, then that is fine.

Cynthia Chmielewski – Okay. Good. My next question is about genomics and genomic data. What kind of genomic testing have you been doing on the population? Are you just doing the standard? If they happen to have myeloma or a precursor condition, is it going to be FISH testing, is it going to be the GEP testing? Are you doing next-generation sequencing, mutation panel as to what type of genomic data are you going to be gathering?

Dr. Sigurdur Kristinsson – So, there are two things that I want to say about the genetic testing. One is, the tumor, if you can say that, the genetics of the…, the…, the MGUS, that is done at the Memorial Sloan-Kettering. They are designing very exciting genetic panels that they will be doing. We will be doing FISH and we will be doing next generation sequencing in all these individuals and gene expression profile as well. We will also put a lot in the freezer because…, I mean, as I talked about this, it does cost a lot, so… I mean we want to do everything at once. We will also have to test…, think of what we are doing. So, we are putting a lot of cells in the freezer and and then we will do these subsequently. Then, there is another thing which I think…, I think its very exciting is that we know that German genetic profile…, profile of…, of the Icelandic population.

Dr. Sigurdur Kristinsson – So, we have a company called deCODE genetics that has done whole genome sequencing the..., of almost the entire Icelandic population. More than 130,000 people have done whole genome sequence because they have, the Icelanders, have donated their DNA to this company. We also know how everyone in Iceland is related to one another and this dates back to the first Icelanders…, Icelanders to step foot in Iceland in 874. So, we know how everyone is related and we know whole genome sequencing or genetic profile for the Icelandic population. So, what we are going to be doing here is we are going to incorporate the risk factors for progression to be able to analyze how different genetic variance that is associated with MGUS or myeloma, how we expect your prognosis or progression risk. So, basically you are born with a tendency to develop myeloma. We know that for those with the color of black race, they have twice the risk of myeloma and MGUS. We also know some genetic variance that are quite common that may give you a risk of maybe 50% increased risk of MGUS and myeloma, but we don't know if this MGUS or myeloma is biologically different from a non-hereditary myeloma. So, this is something I think is very exciting and we are…, we are going to do whole genome sequencing of all the MGUS individuals and I must say we have full faith in that.

Cynthia Chmielewski – Okay.

Dr. Sigurdur Kristinsson – So, there, this is the answer to your question.

Cynthia Chmielewski – Okay. That sounds great. The other thing is, I hear you are cooperating a lot with Dr. Landgen at Memorial Sloan-Kettering. I am wondering about the data that you are going to gather from this trial that you are doing. Who would have access to that data? Will it be just the investigators in the iSTOPMM multiple myeloma trials…

Dr. Sigurdur Kristinsson – Yes.

Dana Holmes – …or will it be the people in the working group, the International Myeloma Working Group? I am just wondering who has access to the data that you going to be finding?

Dr. Sigurdur Kristinsson – So…, so, the data will be kept in a secure computer with several passwords. Every individual in the…, who are participants in the study will be using anonymous code, so no one can be tracked or anything like that and also the data space is only accessible to very few persons in my team, but obviously this is something that is of importance and we love to come up it with every myeloma or MGUS-interested researchers, patients, and other individuals that want to use this data. So, basically what we are going to do is that, if people have some interesting questions to ask, they may contact us, whether data that can be analysed or it can be samples that need to be tested to all kinds of…, all kinds of collaborations, but the data copy goes to the IRB, is to be kept here at the university.

Cynthia Chmielewski – Okay. Thank you. I cannot wait to hear some of the results of this trial. Thank you so much.

Dr. Sigurdur Kristinsson – Thank you very much. Thank you.

Gary Petersen – Thank you, Cindy. Priya, could you… Is there anybody on line with a question?

Priya Menon – Yeah, I think we have Dana on line. Dana, you can please ask your questions.

Dana Holmes – Yes. Hi! It is…, its Dana Holmes. Hi, Dr. Kristinsson! Thank you so much for doing this program. Its really exciting to listen to all of these great plans you have in place.

Dr. Sigurdur Kristinsson – Thank you.

Dana Holmes – I have a question. Concerning the…, the screening tests, am I to understand that for your study, you are going to be using SPEP and free light chains. Is that correct?

Dr. Sigurdur Kristinsson – Yes. So, the SPEP of everyone and free light chain of everyone goes with a suspected M spike or SPEP. We will do immunofixation, everyone with a pathological accuracy ratio, we will do immunofixation.

Dana Holmes – Okay, but…

Dr. Sigurdur Kristinsson – …for successful screening.

Dana Holmes – Yeah. What is though an IFE pick up even the low…, or these M spikes that are too low to actually quantify? So, in essence, if you don't do an IFE first, could you potentially miss a small population of people who have those really low M spikes or is the test that you are doing so sensitive that you wouldn't miss them without an IFE?

Dr. Sigurdur Kristinsson – Yeah. I think that's a very important point. So, I mean every test has its limitations and there are…, I mean we could capture more individuals with the MGUS by doing immunofixation of everyone certainly, but we also know based on data from the Mayo Clinic, for example, that those that are SPEP negative with normal accuracy ratio, if they have something on immunofixation, their risk of progression is much lower than standard MGUS. So, this is like super low risk MGUS, if you will.

Dana Holmes – Ahh! Okay. I see.

Dr. Sigurdur Kristinsson – It.., it…, it does ask a lot of individuals that we will, you know, "have "MGUS." This will probably not be something that they want to scream for in the future, given the low risk. So, if this

acts on a lot of individuals adding anxiety to that and probably of low yield or benefit. So, that was our thinking.

Dana Holmes – Okay. I understand that. Yeah. Am I also to understand that this study hopes to lead to treatment and again, I…, I understand that it would be up to the patient whether they wanted to continue watch and wait or treat but all smoldering patients because right now the IMF is…, is supporting the ASCENT trials for high-risk smoldering patients, but your study hopes to enable and…, and develop a treatment that all smoldering, even the low-risk smoldering patients could participate in?

Dr. Sigurdur Kristinsson – I think… So, the low-risk patients that are…, these are individuals with less than 10% plasma cells in the bone marrow but more than 3 g/dL M spike. So, we… what we are planning is actually smoldering with more than 10% plasma cells in the bone marrow and this is not if we get one biopsy or aspirate with like 11% plasma cells that doesn't mean that they enter the clinical treatment trial. We have protocol for that that these will be re-analysed two or three months later and if they have two consecutive bone marrows with more than 5%.

Dana Holmes – Okay. Yeah. Wow! That's exciting!

Dr. Sigurdur Kristinsson – Yeah, I think that's… So, we are going on in with this early detection, early treatment and because we believe…, strongly believe that this is the way to go.

Dana Holmes – Yes, that's…, that's amazing! I…, I have a smoldering myeloma Facebook group and we have a few of the patients from Dr. Landgren's NIH CRd trial and so they have been finished with it and…, and out of it now and been monitored for the last three years. Indeed, they are all MRD negative and its so exciting for fellow smoldering patients to…, to know that they continue that status. So, obviously that early intervention certainly worked for them. Yeah, Dr. Kristinsson, what would you…

Dr. Sigurdur Kristinsson – Based on the optimum treatment because as we talked about here in the beginning, these are asymptomatic. They are doing great and some people aren't doing great, but for the purpose of myeloma, they are asymptomatic. So, you don't have to give them a very toxic or aggressive treatment that gets them sick with complications, but I think that the plan is coming up where you have really effective therapies with no complications. So, I think the time is right to at least study that. I am not saying that all smoldering patients should be treated or…, I mean this is…, this what we are studying. This is the research question, if early detection and early treatment can cure or prolong the lives of individuals.

Dana Holmes – Yeah. Terrific! Dr. Kristinsson, what would…, once a person has been diagnosed with MGUS, whether it be low risk, intermediate, or high risk, what in your opinion is the best evaluation and monitoring model to follow these MGUS patients because, you know, we have a lot of MGUS patients in these Facebook groups that go to local oncologists and hematologists who are not really familiar with them and so we don't have a lot of MGUS patients. So, they basically just tell them, oh, its a benign, you know, condition, just go home, don't worry about it, don't go on the internet, don't learn anything about it. Come back in a day or two and, you know, we will do another test. So, you know, its very disturbing for me, as a smoldering patient, who was initially diagnosed as having garden variety MGUS only to find out when I pushed for my own bone marrow biopsy initially that indeed it was smoldering myeloma. So, I wonder what would your recommendation be to MGUS patients who have been told to have MGUS. Going forward, what should they be looking for?

Dr. Sigurdur Kristinsson – Yeah. So, this is highlighting the main problem of the literature here. There are no studies. There is no real evidence from prospective randomized clinical trial to guide physicians or patients to the optimal workup or follow up. Now, there is an International Myeloma Working Group, there are lots of experts who can come and make documented guidelines that what they think is the best way to do it and I…, I…, I support these guidelines. I think that is the best we have, but we just have to have… This is really not based on any strong evidence. I guess this is one of the main reasons that they are doing this study with three different arms. So, we want to see if intensive or aggressive workup with follow up leads to more

smoldering, more active myeloma that can be treated earlier, but as of now we just recommend what is recommended by International Myeloma Working Group, but the intervention arm or the…, the third arm of the study may reveal more than it is currently recommended by these guys. So, we have the bone marrow in all individuals, including those with low-risk MGUS. We are doing the CT of skeleton in everyone instead of plain skeletal survey and lots of other intense follow up. So, that is what we think is better, but the key word here is think, but what we want to do is five years from now, we will hopefully know what is the…, the best way because then we will have answers from this study.

Dana Holmes – Okay. Terrific! Thank you so very much for taking my questions.

Dr. Sigurdur Kristinsson – Thank you.

Gary Petersen – And thank you, Dana, as always.

Dana Holmes – Thanks, Gary. Thanks, Priya.

Priya Menon – Bye bye.

Gary Petersen – Doctor, we have got one question from…, that was sent in and its, how realistic is it to anticipate a vaccine or treatment that can be administered at the MGUS stage to prevent progression of the smoldering multiple myeloma or multiple myeloma?

Dr. Sigurdur Kristinsson – Yes. I think that they are supposedly different than story compared to the smoldering because if you are going to offer treatment to a disease or condition that 4% of the Icelandic population have that disease like MGUS and 1% of them will actually turn up with myeloma each year. So in fifth year, only 20% of these individuals will have progressed to myeloma or lymphoma. So, treatment will be recommended for MGUS to prevent oral vaccine then has to have literally no side effects and it has to be very simple. I mean, currently, probably we will have like a vaccine which is one injection which will prevent myeloma in everyone. We are reading up there, but we can talk about three things in MGUS case. We cannot treat 4% of the population with any drug, I think, but in the interim what we hope to gain from this study and a lot of MGUS research that we are doing, we want to try to optimize the prognostic scores so we can identify high-risk MGUS compared to the current prognostic scores where we can identify high-risk MGUS and also in smoldering category.

Gary Petersen – I recently saw Dr. Kumar From Mayo Clinic on a retrospective analysis and that analysis indicated that 30% of patients don't make it a year and so he said…, and part of it was from delayed diagnosis and part of it was because, you know, that you needed an expert who treats you and I think that was clearly very important. The other thing is myeloma U.K. put out an analysis and it said that in 1 in 5 patients don't last two months.

Dr. Sigurdur Kristinsson – yeah we have seen that in our studies. Early death is really high and this is due to infections. So, when we go to conferences and listen to discussions or outcomes of treatment, we sometimes hear up a patient who has got like 15 lines of therapy at different ages. But when we go out and see, at a lot of places actually only one-third of patients get third plan of therapy. So, most patients diagnosed with myeloma do not get more than three or four lines of therapy.

Gary Petersen – Another thing that I happened to see, again I think it might have been an European analysis which said, and Dr. Morgan had stated this and he says that he called it a bit of a scandal, he would in his British accent, that myeloma patients, exact 25% of them, it takes one year from symptom to diagnosis.

Dr. Sigurdur Kristinsson – Yes.

Gary Petersen – You think about that and he also recognized that apparently there has been also an

analysis that said without treatment the average life expectancy is less than a year. So, effectively, 25% of patients at data diagnosis and that's a bit of a scandal. So, all your work is going to help eliminate that if we can just catch it early.

Dr. Sigurdur Kristinsson – Yes.

Gary Petersen – So, its so exciting, I think…, you know that….

Dr. Sigurdur Kristinsson – I think a lot of nonspecific signs and symptoms like backache and mild anemia and…, and these symptoms are so vague and they can mean a lot of things. When you think about it, if you take a random 70-year-old, lots of them have a little bit of ache and have pains somewhere or other and their hematocrit or hemoglobin is a little bit low and you cannot really suspect myeloma in all these individuals. So, unfortunately, this is the case. These patients are not diagnosed. There is doctor delay and there is patient delay and screening will potentially eliminate that.

Gary Petersen – Priya, any other questions from our callers?

Priya Menon – None. That's all, Gary. Thank you, Dr. Kristinsson, for your time and sharing all this information with us. We are almost at the end of our time.

Dr. Sigurdur Kristinsson – I am very excited. Thank you.

Priya Menon – Gary, Matt, Yelak, and Cindy, thank you so much for your information; and Dr. Kristinsson, we wish the study all the very best. The transcript will be available on the CureTalks website and please visit curetalks.com for more details and upcoming shows. Thank you, everyone. Have a nice day.

Gary Petersen – Thank you so much, doctor.

Dr. Sigurdur Kristinsson – Thank you.